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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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STEADMAN, DAVID J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,951	ANDERTON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,26,27,31-36,38-46 and 53-55* is/are pending in the application.

4a) Of the above claim(s) *31,33-35,40,43-46,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,23,26,27,32,36,38,39,41,42 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 22-23, 26-27, 31-36, 38-46, and 53-55 are pending in the application.

[2] Applicant's amendment to the claims, filed on 2/3/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 2/3/09, is acknowledged.

[4] Receipt of an information disclosure statement, filed on 2/3/09, is acknowledged.

[5] Applicant's arguments filed on 2/3/09 in response to the Office action mailed on 10/3/08 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Rejections and/or objections directed to claims 24-25 and 28-29 are obviated in view of the instant amendment to cancel these claims.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[7] Applicant continues to traverse the lack of unity requirement, arguing at p. 7 of the instant remarks that claims 33-35 share the same or corresponding special technical feature as that of the elected invention.

Applicant's argument is not found persuasive. Here, the inventions of elected Group I and non-elected Group II have different special technical features. The special

technical feature of Group I is a method for screening for substances that are capable of inhibiting CK1 phosphorylation of tau. However, although claims 33-35 of Group II depend from claim 22 of Group I, claims 33-35 require the use of a "combination of kinases", including those specifically set forth in claims 34 and 35. Thus, the special technical feature of Group II is not in identifying an inhibitor of CK1 phosphorylation of tau, but in identifying an inhibitor of a combination of kinases, *e.g.,* those recited in claims 34-35. According to the specification, a number of kinases phosphorylate tau (*e.g.,* p. 38) and the residues where tau is phosphorylated are not exclusive to any particular kinase, *i.e.,* there is at least some overlap with respect to the residues that are phosphorylated by CK1, CK2, GSK-3, and PKA. As such, an inhibitor identified according to the method of claims 33-35 using a combination of kinases would not necessarily inhibit CK1 phosphorylation of tau, but any one or more of the other kinases of the combination. Also, according to the disclosure of the specification, "combinations of kinases can result in phosphorylation at new sites" relative to phosphorylation using any single kinase of the combination, including CK1 (p. 39, lines 13-22). See also the reference of Hanger et al. (*J. Biol. Chem.* 282:23645-23654, 2007) at p. 23650, Figure 5, comparing phosphorylation sites of CK1 and a combination of CK1, CK2, PKA, and GSK-3beta.

At least for reasons set forth below, the claimed invention is shown to lack an inventive step and thus the technical feature of Group II is not a contribution over the prior art. Consequently, the inventions of Groups I-VII lack unity of invention and the requirement is still deemed proper and is therefore made FINAL.

[8] Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/10/08.

[9] Claims 22-23, 26-27, 32, 36, 38-39, 41-42, and 55 are being examined on the merits. Claims 22, 32, 39, and 55 are being examined only to the extent the claims read on the elected subject matter.

Information Disclosure Statement

[10] The reference cited in the information disclosure statement filed on 2/3/09 has been considered by the examiner. A copy of Form PTO/SB/08 is attached to the instant Office action. The first page of the IDS has been lined through because no references are cited.

Claim Objections

[11] Claim 22 is objected to in the recitation of "80% sequence identity" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.*, "80% amino acid sequence identity".

[12] Claim 22 is objected to in the recitation of "the amino acid sequence set out between amino acids 1 and 428 inclusive of SEQ ID NO:1" and "the amino acid sequence set out between amino acids 1 and 441 inclusive of SEQ ID NO:2". According to the sequence listing filed on 9/24/07, SEQ ID NO:1 is 428 amino acids and SEQ ID

NO:2 is 441 amino acids and thus, the recitation of "the amino acid sequence set out between amino acids 1 and 428 inclusive" and "the amino acid sequence set out between amino acids 1 and 441 inclusive" with respect to SEQ ID NO:1 and 2 is redundant. In order to substantially improve claim form, it is suggested that the noted phrases be amended to recite "the amino acid sequence of SEQ ID NO:1" and "the amino acid sequence of SEQ ID NO:2".

[13] Claim 55 is objected to as not ending with a period. Also, the Markush group should include an "and" prior to "S435". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

[14] Claims 22-23, 26-27, 32, 36, 38-39, and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 (claims 23, 26-27, 32, 36, 38-39, and 41-42 dependent therefrom) is indefinite because the claim requires contacting CK1 with a tau protein having greater than 80% identity to SEQ ID NO:2 and determining phosphorylation at one or more residues as recited in the claims. However, the claim does not require that the tau protein have any of the recited residues and it is unclear as to whether the tau protein having greater than 80% identity to SEQ ID NO:2 is or is not required to have the recited residues. Also, the preamble of claim 22 recites "the tau protein comprises one or more phosphorylation sites" and part (a) of claim 22 requires the CK1 to be "capable of phosphorylating the site(s) of the tau protein in the absence of the candidate

substance". Because the claim does not require that the tau protein have any of the residues as recited in part (b), a skilled artisan would recognize that the CK1 is not required to phosphorylate the tau protein at one or more of the residues recited in part (b). In addition to variation in the tau protein sequence, it is noted that the claim allows for variation in the sequence of CK1. Since claim 22 allows for sequence variation in the CK1 and tau proteins, the CK1 is not required to phosphorylate tau at any of the residues recited in part (b), and the tau protein is not required to have any of the residues recited in part (b), an alteration in the sites of tau that are phosphorylated by CK1 may be merely a function of altering the sequence(s) of the CK1 relative to SEQ ID NO:1 and/or altering the sequence of the tau relative to SEQ ID NO:2 and not an indication of inhibition by a candidate compound. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[15] The written description rejection of claims 22-23, 26-27, 32, 36, 38-39, and 41-42 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [14] beginning at p. 7 of the 10/3/08 Office action. Claim 55 is included in the instant rejection as being dependent upon claim 22. Thus, claims 22-23, 26-27, 32, 36, 38-39, 41-42, and 55 are rejected herein.

RESPONSE TO ARGUMENT: Although applicant acknowledges the instant rejection (instant remarks, p. 8, top), the examiner can find no remarks specifically

traversing the instant rejection. The examiner assumes the applicant's intent is for the amendment to claim 22 to address the instant rejection, namely limiting the genus of CK1 and tau proteins to those that are "greater than 80% sequence identity" to SEQ ID NO:1 and 2, respectively.

Applicant's argument is not found persuasive. Claim 22 is drawn to a method of screening for substances that are capable of inhibiting the phosphorylation of a tau protein by casein kinase 1 (CK1). As noted in the prior Office action, the specification discloses, "In the present invention, derivatives of the tau proteins, kinases (especially CK1 kinase...have an amino acid sequence which differs by one or more amino acid residues from the wild-type amino acid sequence, by one or more of addition, insertion, deletion and substitutions of one or more amino acids. Thus, variants, derivatives, alleles, mutants and homologues...are included" (p. 17, lines 10-17). As noted above, claim 22 has been amended to limit the genus of CK1 and tau proteins to those that are "greater than 80% sequence identity" to SEQ ID NO:1 and 2, respectively. The function of the genus of CK1 proteins is limited to those that are "capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance", wherein the tau phosphorylation site(s) is/are (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435. The genus of tau proteins is unlimited with respect to function.

The specification discloses the reduction to practice of a single representative species of the genus of recited CK1 polypeptides that is capable of phosphorylating tau

at one or more residues selected from those noted above, *i.e.*, SEQ ID NO:1. The specification discloses the reduction to practice of a single representative species of the genus of recited tau polypeptides that are capable of being phosphorylated at one or more residues selected from those noted above, *i.e.*, SEQ ID NO:2. There are no other drawings or structural formulas disclosed of a CK1 and/or tau polypeptide encompassed by the claims. However, with the aid of a computer, one of skill in the art could conceivably identify all of the amino acid sequences that have at least 80% amino acid sequence identity with the amino acid sequences of SEQ ID NO:1 and 2. It is noted that at 20% variance relative to SEQ ID NO:1, this allows for up to about 85 amino acid changes. However, there is no prior-art or disclosed teaching regarding which 20% of the amino acids can vary from SEQ ID NO:1 and still result in a protein that retains the capability of phosphorylating tau at one or more residues selected from those noted above and there is no disclosed or art-recognized correlation between any structure other than SEQ ID NO:1 and being capable of phosphorylating tau at one or more residues selected from those noted above. Also, there is no prior-art or disclosed teaching regarding which 20% of the amino acids can vary from SEQ ID NO:2 and still result in a protein that retains the capability of being phosphorylated at one or more residues selected from those noted above and there is no disclosed or art-recognized correlation between any structure other than SEQ ID NO:2 and being capable of being phosphorylated at one or more residues selected from those noted above.

Given what is known in the art about the likely outcome of substitutions on structure, conservation of structure is not necessarily a surrogate for conservation of

function. In this case, there is no disclosed correlation between structure and function. Here, it is not enough that the genus of CK1 variants maintain serine/threonine kinase activity or the ability to generally phosphorylate tau. Instead, the genus of CK1 proteins is required to maintain the ability to phosphorylate tau at one or more residues selected from those noted above and the genus of tau proteins is required to maintain the ability of being phosphorylated by CK1 at one or more residues selected from those noted above. There is no general knowledge in the art about CK1 phosphorylation of tau at one or more residues selected from those noted above to suggest that general similarity of structure confers the activity. The instant specification discloses that CK1, GSK-3beta, CK2, and PKA each preferentially phosphorylates serine/threonine residues of tau of SEQ ID NO:2, with some, but not complete overlap with respect to the residues phosphorylated by each of CK1, GSK-3beta, CK2, and PKA (see, *e.g.*, p. 45, Table 3). For example, according to Table 3, CK1 and GSK-3beta phosphorylate S289 of the tau of SEQ ID NO:2, while CK2, and PKA do not. This evidence indicates that there are structural features of CK1 and/or tau that enable phosphorylation of certain tau residues, while the other kinases of GSK-3beta, CK2, and PKA are or are not able to phosphorylate the same tau residues. However, the specification fails to identify those amino acids or regions of CK1 and/or tau that confer the activity of CK1 being capable of phosphorylating tau at one or more residues selected from those noted above.

Accordingly, one of skill in the art would not accept the disclosure of SEQ ID NO:1 as being representative of other CK1 proteins that have the activity of phosphorylating tau at the residues noted above. Also, one of skill in the art would not

accept the disclosure of SEQ ID NO:2 as being representative of other tau proteins that are phosphorylated by CK1 at the residues noted above. As such, the specification, taken with the pre-existing knowledge in the art of amino acid substitution, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

[16] The scope of enablement rejection of claims 22-23, 26-27, 32, 36, 38-39, and 41-42 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [15] beginning at p. 10 of the 10/3/08 Office action. Claim 55 is included in the instant rejection as being dependent upon claim 22. Thus, claims 22-23, 26-27, 32, 36, 38-39, 41-42, and 55 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 12 of the instant remarks, applicant argues: 1) the claims are not drawn to a nucleic acid, but to a screening method using CK1 that is capable of phosphorylating tau at the recited residues and further using tau that is a substrate for CK1 and 2) based on the guidance provided in the specification and prior art, only routine experimentation is required to identify those mutants of CK1 as encompassed by the claims that maintain the activity of phosphorylating tau at the recited residues.

Applicant's argument is not found persuasive. Claim 22 is drawn to a method of screening for substances that are capable of inhibiting the phosphorylation of a tau protein by CK1. The scope of CK1 variants has been limited to those that have greater than 80% amino acid sequence identity to SEQ ID NO:1 and are "capable of

phosphorylating the site(s) of the tau protein in the absence of the candidate substance". However, as noted above, the scope of CK1 variants is not required to phosphorylate at least one of the residues as recited in claim 22, part (b). The scope of tau proteins has been limited to those that have "greater than 80% sequence identity" to SEQ ID NO:2 and the method requires determining CK1 phosphorylation at one or more tau residues (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435. However, as noted above, the scope of tau proteins used in the claimed method is not required to have any of the recited amino acids upon which the determining step is based.

Here, the specification fails to provide guidance for using the claimed method when the CK1 variant of SEQ ID NO:1 does not phosphorylate tau at any one of the residues as recited in claim 22, part (b) and/or the tau protein does not have at least one of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435. Moreover, the instant specification fails to provide any guidance for using the claimed method when the CK1 variant of SEQ ID NO:1 does not phosphorylate tau at any of the residues as recited in claim 22, part (b) and the tau protein does not have at least one of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435. Also, it is noted that since claim 22 allows for sequence variation in the CK1 and

tau proteins, the CK1 is not required to phosphorylate tau at any of the residues recited in part (b), and the tau protein is not required to have any of the residues recited in part (b), an alteration in the sites of tau that are phosphorylated by CK1 may be merely a function of altering the sequences of the CK1 relative to SEQ ID NO:1 and/or altering the sequence of the tau relative to SEQ ID NO:2 and not an indication of inhibition by a candidate compound. At least for these reasons, it is the examiner's position that the specification fails to teach how to use the full scope of the claimed invention.

Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

[17] Claim(s) 22, 26, 32, 36, 38-39, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa et al. (*J. Biol. Chem.* 267:17047-17054, 1992; hereafter referred to as "Hasegawa"), Curran et al. (US Patent Application Publication 2002/0172990 A1; hereafter referred to as "Curran"), Hanger et al. (*J. Neurochem.*

71:2465-2476, 1998; cited in the IDS filed on 10/3/08; hereafter referred to as "Hanger"), Morishima-Kawashima et al. (*J. Biol. Chem.* 270:823-829, 1995; hereafter referred to as "Morishima"), and Anderton et al. (US Patent 5,994,084; cited in the Form PTO-892 mailed on 10/3/08; hereafter referred to as "Anderton").

CLAIM INTERPRETATION: Claim 22 has been amended to recite the limitation, "determining whether...the candidate substance inhibits said phosphorylating of the tau protein, by identifying the site(s) at which the casein kinase 1 phosphorylates the tau protein..." in part (b). In the context of the claim, the term "identifying" has been interpreted as "looking for" or "seeking to know" the sites of tau phosphorylation by CK1 without *a priori* knowledge of such sites. As such, the "identifying" step has been broadly but reasonably interpreted as analyzing the full sequence of tau for CK1 phosphorylation sites since one analyzing the full sequence of tau for CK1 phosphorylation sites would be looking for or seeking to know any and all phosphorylation sites of tau, which necessarily includes those recited in part (b) of claim 22.

At the time of the invention, methods for screening for inhibitors of CK1 activity were known in the prior art. For example, Chijiwa teaches a method for identifying inhibitors of CK1 using casein as a substrate and measuring CK1 activity in the presence of varying concentrations of inhibitor compound (p. 4924, column 2 and p. 4925, Table I and Figure 1). Meijer teaches identification of a potent inhibitor of CK1, hymenialdisine, and inhibition of CK1 using analogs thereof (p. 54, Table 2) and shows inhibition of CK1 phosphorylation of presenilin-2 by hymenialdisine (p. 54, Figure 3).

Meijer further teaches "The kinases responsible for hyperphosphorylation of tau...observed in AD certainly constitute reasonable screening targets" and teaches that CK1 is a "major" kinase in this process (p. 61, column 1, top).

Also, at the time of the invention, it was well-known in the prior art that CK1 was a therapeutic target by virtue of its activity of phosphorylating tau. For example, the reference of Lau teaches casein kinase I can phosphorylate tau, is tightly associated with paired helical filaments purified from Alzheimer's disease brains, three CK1 isoforms are upregulated in Alzheimer's disease brain, and that CK1 may be linked to tau pathology in Alzheimer's disease (p. 401, column 2, top). Lau further teaches "Since tau hyperphosphorylation is believed to be a critical step in neurofibrillary degeneration in AD, tau protein kinases become obvious therapeutic targets" (p. 403, column 2, bottom) and that since tau phosphorylation appears to be the primary contributor of paired helical filament/neurofibrillary tangle formation and microtuble disruption, inhibition of tau phosphorylation has been proposed as a therapeutic target" (p. 405, paragraph bridging columns 1-2). Additionally, Castro teaches "...such aberrant phosphorylation of tau, determined by the effects of different protein kinases...appears to compromise on its ability to bind and stabilise microtubules and this may contribute to [Alzheimer's disease] pathology" (p. 1520, column 1, bottom) and that casein kinase I has "been shown to phosphorylate certain tau residues *in vitro*" (p. 1520, column 2, middle). According to Castro, "Although the search for tau protein kinase inhibitors is an active field, at the moment few compounds are known with this inhibitor enzymatic property" (p. 1521, column 2, bottom). With regard to identifying tau phosphorylation

inhibitors, Castro teaches that *in vitro* assays using GSK-3 – another tau kinase – have been extended to a high throughput methodology for screening selective inhibitors (p. 1521, column 2, bottom).

At the time of the invention, it was well-known in the prior art that tau is phosphorylated by casein kinase I (CK1) from various eukaryotic sources. For example, Singh teaches human tau protein is phosphorylated by bovine brain, bovine kidney, and yeast CK1 (p. 1421, Figures 1 and 3). Also, Kuret identifies a paired helical filament kinase as CK1 (p. 2506, abstract), teaches tau phosphorylation by human CK1 (p. 2508, Figure 1), and that a CK1- specific inhibitor inhibited a paired helical filament-associated CK1 polypeptide (p. 2509, column 2, middle).

While the combination clearly *suggests* screening for CK1 inhibitors of tau protein, however, there appears to be no *express* teaching of a method of using tau as a substrate in a screening method for CK1 inhibitors of tau phosphorylation.

At the time of the invention, methods for identifying a phosphorylation site of a kinase substrate were well-known in the prior art. In this regard, Hasegawa (p. 17048), Hanger (p. 2467), and Morishima (p. 824) teach identifying phosphorylation sites on paired helical filament tau by mass spectroscopy.

Also, at the time of the invention, *in vitro* kinase assays were well-known in the prior art. For example, Anderton et al. (US Patent 5,994,084) teaches an *in vitro* kinase assay using tau as a substrate and using a kinase "capable or thought to be capable of phosphorylating tau" and analysis of the phosphorylation state of tau (column 4, lines 30-35 and column 17). Also, Curran teaches using the phosphorylation state of the

identified phosphorylation sites for screening modulator compounds in an *in vitro* inhibition assay (paragraphs 39-40).

At the time of the invention, the sequences of CK1 and tau were well known. For example, Graves teaches cloning of a nucleic acid encoding a rat testis CK1 polypeptide (p. 6395-6396) that has a nucleotide sequence (p. 6397) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix A sequence alignment of the prior Office action). Graves further teaches recombinant production of this polypeptide (p. 6397, paragraph bridging columns 1-2) and use of the polypeptide in an inhibition assay (p. 6398, Figure 6). Vitek teaches cloning of a nucleic acid encoding a human tau polypeptide (Example 7, beginning at column 12) that has a nucleotide sequence (SEQ ID NO:7) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix B sequence alignment). Vitek further teaches recombinant production of this polypeptide (Example 10 beginning at column 14) and use of the polypeptide in an inhibition assay (p. 6398, Figure 6).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Hasegawa, Hanger, Morishima, Curran, and Anderton to use the polypeptides of Graves and Vitek in an *in vitro* kinase assay to screen for inhibitors using the well-known phosphorylation detection method of Hanger or Morishima to detect inhibition of tau phosphorylation by CK1. By practicing such method, one would have been looking for the phosphorylation sites of the full-length tau protein, which would include those sites recited in claim 22, part (b). One would have been motivated to screen for

inhibitors of tau phosphorylation by CK1 because of the teachings of Lau and Castro as described above. One would have been motivated to use the polypeptides of Graves and Vitek in such an inhibitor screen because these are biologically relevant CK1 and tau polypeptides. One would have been motivated to use the well-known phosphorylation detection method of Hanger or Morishima to detect inhibition of tau phosphorylation by CK1 because such method does not require affinity reagents required in other detection methods, *e.g.,* immunoassay. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Hasegawa, Hanger, Morishima, Curran, and Anderton because of the results of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Hanger, Morishima, Curran, and Anderton to use the polypeptides of Graves and Vitek in an *in vitro* kinase assay to screen for inhibitors using the method of Hanger or Morishima to detect inhibition of tau phosphorylation by CK1. Therefore, the method of claims 22, 26, 32, 36, 38-39, and 55 would have been obvious to one of ordinary skill in the art at the time of the invention.

[18] Claim(s) 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Anderton as applied to claims 22, 26, 32, 36, 38-39, and 55 above and further in view of Ford et al. (*Prot. Exp. Purif.* 2:95-107, 1991; hereafter referred to as "Ford"). Claims 23 and 27 exclude the "wild-type" CK1 and tau

polypeptides of SEQ ID NO:1 and 2, limiting claim 22 to a fragment or derivative of SEQ ID NO:1 and 2.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Anderton are set forth above. Of note is that Castro teaches the concept of using high throughput assays for identifying tau kinase inhibitors. The combination does not expressly teach or suggest using a fragment or derivative of SEQ ID NO:1 or 2 as encompassed by the claims.

Ford teaches the use of affinity tags for facilitating purification of recombinant proteins, including a polyhistidine tag (p. 100).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, Anderton and Zhu to include a polyhistidine tag of Ford with a recombinant CK1 and tau for use in an *in vitro* kinase assay to screen for inhibitors using the well-known phosphorylation detection method of Hanger or Morishima to detect inhibition of tau phosphorylation by CK1. One would have been motivated to do this because of the advantages as taught by Ford. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Ford to include a polyhistidine tag of Ford with a recombinant CK1 and tau for use in an in vitro kinase assay because of the results of Meijer, Chijiwa, Singh, Kuret Graves, Vitek, Hasegawa, Hanger, Morishima, and Ford.

Therefore, the method of claims 23 and 26 would have been obvious to one of ordinary skill in the art at the time of the invention.

[19] Claim(s) 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Anderton as applied to claims 22, 26, 32, 36, 38-39, and 55 above and further in view of Zhu. Claims 41-42 limit the screening of the method of claim 22.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Anderton are set forth above. Of note is that Castro teaches the concept of using high throughput assays for identifying tau kinase inhibitors. The combination does not expressly teach or suggest screening according to claims 41-42.

Zhu teaches "In the past, studies of protein activities have focused on studying a single protein at a time, which is often time-consuming and expensive" (p. 40, abstract). Zhu teaches the use of protein chips for protein kinase assay by, *e.g.,* attaching a substrate to a microwell plate and assaying kinase activity (p. 42, paragraph bridging columns 1-2 and p. 43, Figure 2). According to Zhu, "Coupled with mass-spectrometric identification, protein chips might also have wide application in drug discovery…Proteins and small-molecule ligands can be bound to proteins immobilized on a protein chip and the bound molecules identified using…mass spectroscopy" (p. 43, column 1, bottom).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, Anderton, and Zhu to use a protein chip and mass spectroscopy in a CK1 inhibitor screening method with tau protein as substrate. One would have been motivated to do this because Zhu teaches advantages of using protein chips as noted above and Castro suggests using a high throughput assay for identifying inhibitors of a tau kinase. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, Anderton and Zhu to use a protein chip and mass spectroscopy in a CK1 inhibitor screening method with tau protein as substrate because of the results of Meijer, Chijiwa, Singh, Kuret Graves, Vitek, Hasegawa, Hanger, Morishima, Anderton, and Zhu. Therefore, claims 41-42, drawn to a method as described and interpreted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: Beginning at p. 14 of the instant remarks, applicant argues: 1) the rationale for combining references is "dubious at best" because the prior art fails to identify CK1 as a valid therapeutic target; 2) asserting Graves teaches an inhibition assay is "disingenuous" because Graves only teaches an inhibition assay using a known CK1 inhibitor, and is not a screen for candidate CK1 inhibitors; 3) Vitek provides no motivation to screen for kinase inhibitors; and 4) the amended claims "now positively call for identifying the site(s) at which the CK1 phosphorylates the tau

protein, followed by a Markush group of such sites", which are not expressly taught by the cited prior art references.

Applicant's argument is not found persuasive. Regarding argument 1), in reading the examiner's cited teachings of at least Lau and Castro (prior Office action at pp. 17-18), one of ordinary skill in the art would clearly recognize CK1 as a therapeutic target of interest by virtue of its activity of phosphorylating tau. See also the reference of Singh, which teaches that phosphorylation of tau by CK1 "converts it to an abnormal Alzheimer-like state" (p. 1420, title) with CK1 being the "most successful" among a number of other tau kinases in inducing Alzheimer-like epitopes (p. 1420, column 2, middle). Numerous other prior art references support this position, yet in the interest of brevity, the examiner has not included these references in the instant rejection. While applicant points to two particular teachings of Castro and Lau in asserting the examiner's rationale is "dubious at best", the combined teachings nonetheless teach CK1 is a therapeutic target of interest. Here, applicant has failed to present any evidence or rationale that would teach away from combining the cited references.

Regarding arguments 2) and 3), applicant's position appears to be that the claimed invention is non-obvious solely in view of the reference of Graves or Vitek. The examiner agrees with this position. However, the instant rejection is based on a combination of references, not solely on the reference of Graves or Vitek. Applicant is urged to consider the combined teachings rather than any single reference or subset of references. The combined references clearly suggest screening for inhibitors of CK1 phosphorylation of tau. The reference of Graves is cited as teaching a biologically

relevant CK1 polypeptide and the reference of Vitek is cited as teaching a biologically relevant tau polypeptide.

With respect to applicant's assertion that the examiner is "disingenuous" because the method of Graves used "a known inhibitor of CK1" and was "not to screen for candidate inhibitors", it is noted that nowhere does the examiner characterize the assay of Graves as a "screen for candidate CK1 inhibitors" as asserted by applicant. Moreover, it is noted that the claims do not limit the "candidate substance" to exclude a "known inhibitor of CK1".

Regarding argument 4), the examiner acknowledges the amendment to claim 22 to recite an "identifying" step. As noted above, claim 22 has been amended to recite the limitation, "determining whether…the candidate substance inhibits said phosphorylating of the tau protein, by identifying the site(s) at which the casein kinase 1 phosphorylates the tau protein…" in part (b). In the context of the claim, the term "identifying" has been interpreted as "looking for" or "seeking to know" the sites of tau phosphorylation by CK1 without *a priori* knowledge of such sites. As such, the "identifying" step has been broadly but reasonably interpreted as analyzing the full sequence of tau for CK1 phosphorylation sites. When one analyzes phosphorylation using a method that globally detects phosphorylated residues of the full sequence of tau, *e.g.*, the method of Hasegawa, Hanger, or Morishima, which were well-known at the time of the invention and require no more than routine experimentation, one is necessarily analyzing any and all sites of phosphorylation of tau, including those that are recited in the claims.

Claim Rejections – Double Patenting

[20] Claims 22, 26, 32, 36, 38-39, and 55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 (same as the reference of Anderton) in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Vitek, Hasegawa, Curran, Hanger, and Morishima. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Vitek, Hasegawa, Curran, Hanger, and Morishima are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CK1 of Graves and use the tau of Vitek in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 with CK1 of Graves and use the tau of Vitek in the method of the '084

patent because of the results of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Vitek, Hasegawa, Curran, Hanger, and Morishima.

[21] Claims 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Zhu. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Zhu are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CK1, use the tau of Vitek, and use the method of Zhu in detecting the phosphorylation of tau in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 with CK1, use the tau of Vitek, and use the method of Zhu in detecting the phosphorylation

of tau in the assay of claims 6-9 and 12 of the '084 patent because of the results of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima, and Zhu.

RESPONSE TO ARGUMENT: Beginning at p. 17 of the instant remarks, applicant argues the claims of the '084 patent require CK1 instead of a GSK-3 protein and further requires "identifying" the occurrence of phosphorylation at the specific sites recited in claim 22. Applicant reiterates their remarks addressing the rejections under 35 U.S.C. 103(a).

Applicant's argument is not found persuasive. In regard to applicant's argument that there are differences between the claims of the '084 patent and the instant claimed invention, substituting GSK-3 with CK1 is an obvious variation in view of the prior art, which teaches that CK1, along with GSK-3, is a tau kinase. See, *e.g.*, Castro at p. 1520, column 2, middle.

Regarding the limitations of the "determining"/"identifying" step, as noted above, in view of a broad, but reasonably interpretation of the claims and in using a well-known and routine phosphorylation detection method, one is necessarily analyzing any and all sites of phosphorylation of tau, including those that are recited in the claims.

In response to applicant's arguments addressing the rejection under 35 U.S.C. 103(a), the examiner's response is set forth above, maintaining the position that the claimed invention would have been obvious at the time of the invention.

Conclusion

[22] Status of the claims:

- Claims 22-23, 26-27, 31-36, 38-46, and 53-55 are pending.
- Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from consideration.
- Claims 22-23, 26-27, 32, 36, 38-39, 41-42, and 55 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/

Primary Examiner, Art Unit 1656